Muscle Weakness and Atrophy

Clinical and Laboratory Evaluation

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■ *A thorough family history, the age at the time of onset and detailed information regarding the rate, mode of progression and distribution of weakness is needed for evaluation of patients with weakness and atrophy. Associated findings such as dermal lesions, tenderness, myotonia and fasciculations should also be noted.*

The major diagnostically useful laboratory tests are electromyography, nerve conduction, serum enzyme levels and muscle biopsy.

Each clinical and laboratory finding should be categorized in terms of its neuro-anatomical origin, since weakness may result from disturbances in the corticospinal pathways, the lower motor neuron, the myoneural junction and the muscle.

WEAKNESS IS THE predominant finding in most disorders of the skeletal muscle, but may also result from disturbances in the corticospinal pathways, the lower motor neuron including the anterior horn cell and its peripheral nerve, and the myoneural junction. The differential diagnosis of neuromuscular diseases depends primarily on a careful clinical history and physical examination[7,8] (Table 1), and laboratory tests may provide further valuable information.

The history should include a thorough family survey in search of any similar conditions and detailed information about the age of onset and the rate and mode of progression of the weakness (Tables 2 and 3). Clinical assessment should stress the distribution of weakness and the presence or absence of associated findings such as atrophy, hypertrophy, fasciculations, muscle tenderness, upper motor neuron signs, contractures, myotonia and dermal lesions (Tables 4 and 5).

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Each finding should be categorized in terms of its neuro-anatomical site[6] (Table 6). Weakness due to lesions in the corticospinal pathways rarely causes confusion in diagnosis with lesions of the lower motor neuron or muscle, since the presence of other signs of brain or spinal cord damage is readily recognized. Classical disease of the anterior horn cell is characterized by atrophy, fasciculations, hypoactivity or absence of reflexes, and usually a distal distribution of loss of strength. If the peripheral nerve is involved, associated sensory complaints are commonly present. Primary diseases of the muscle are also characterized by atrophy and diminution or absence of reflexes, but weakness is usually most severe in the proximal musculature. Myasthenia gravis, the only significant disorder associated with dysfunction of the myoneural junction, is usually characterized by involvement of the extraocular and bulbar musculature early in the disease process. In this disease there is little or no atrophy, and although the use of voluntary muscles is rapidly fatiguing, strength returns on rest. Due to its course, which is often variable, it may be mistaken for a psychogenic disturbance.

Indeed, the words *weakness, tiredness* and *fa-*

tigue obtained from the patient are quite vague and non-specific. They do not necessarily denote a disorder of the neuromuscular system but may relate to a conversion reaction or to depression or malingering. Psychogenic weakness, however, is usually accompanied by specific physical responses and inconsistencies.[12] A ratchet or cogwheel response is often found during manual muscle testing. In true neuromuscular weakness, the patient exerts maximal efforts throughout the test, and the weak muscles "give away" smoothly.

Inconsistencies also become apparent during the examination of the patient with psychogenic weakness or paralysis. During manual muscle testing in the recumbent position, the patient will be unable to resist a few pounds of force to the knee and hip flexors and extensors but be able to do deep knee bends without difficulty. Muscles which are apparently flaccid may suddenly contract when the patient performs functional or unusual movements such as crawling or walking backward. The patient with a conversion reaction may also perform many of the activities in a slow and laborious manner and frequently carries out simple acts with an overflow of activity into unrelated areas. The inconsistency is apparent since most of the functional tests such as knee bends require considerably more strength when done slowly.

Evaluation of weakness includes careful observation of the patient in a variety of positions and activities as well as an evaluation of individual muscle strength and range of joint motion. A thorough knowledge of functional anatomy is necessary since the patient with a slowly progressive neuromusculer disorder has often learned to substitute normal for weak muscle groups. To the inexperienced observer the resulting activity pattern will often appear to be completely normal.

Observation of the patient as well as details from the history can give valuable clues as to the distribution of weakness.[8] Loss of strength in the neck and trunk can be detected by the way the

TABLE 1.—*Steps in Clinical and Laboratory Evaluation of Weakness*

Detailed history
Family survey
Age of onset
Rate and mode of progression
Clinical assessment
Distribution of weakness
Tenderness
Contractures
Myotonia
Fasciculations
Upper motor neuron signs
Cramping
Hypertrophy
Dermal lesions
Myoedema
Mental retardation
General laboratory survey
Electromyography and nerve conduction
Serum enzymes
Biopsy

TABLE 2.—*Types of Inheritance in Disorders in which Weakness is the Predominant Feature*

Dominant
Facioscapulohumeral dystrophy
Myotonic dystrophy
Distal dystrophy
Proximal familial muscular atrophy
Peroneal muscular atrophy
Potassium periodic paralysis
Autosomal recessive
Infantile spinal muscular atrophy
Limb-girdle dystrophy
Peroneal muscular atrophy
Sex-linked recessive
Duchenne muscular dystrophy
Peroneal muscular atrophy

TABLE 3.—*Examples of Neuromuscular Disorders by Age at Onset*

Birth	Adults
Infantile spinal muscular atrophy	Limb-girdle dystrophy
Benign infantile hypotonia	Facioscapulohumeral dystrophy
Congenital muscular dystrophy	Distal dystrophy
Congenital myopathies	Motor system disease
Early Childhood	Myotonic dystrophy
Duchenne muscular dystrophy	Thyrotoxic myopathy
Glycogen storage disease	Potassium periodic paralysis
Infantile spinal muscular atrophy	Sarcoid myopathy
Congenital myopathies	Peroneal muscular atrophy
Late childhood and adolescence	Proximal familial muscular atrophy
Limb-girdle dystrophy	Any age
Congenital myotonia	Trichinosis
Potassium periodic paralysis	Dermatomyositis and polymyositis
Peroneal muscular atrophy	Polyarteritis
	Myasthenia gravis
	Drug-induced myopathy

TABLE 4.—*Examples of Neuromuscular Disorders by Chief Site of Weakness*

Proximal muscle groups	
Muscular dystrophies	Myositis
Thyrotoxic myopathy	Sarcoid myopathy
Familial proximal muscular atrophy	
Distal muscle groups	
Motor system disease	Peroneal muscular atrophy
Myotonic dystrophy	Distal muscular dystrophy
Other peripheral motor neuropathy	
Proximal or distal or both	
"Floppy infant"	Myasthenia gravis
Poliomyelitis	Periodic paralysis
Steroid myopathy	Dystrophic ophthalmoplegia

TABLE 5.—*Findings Often Associated with Disorders in Which Weakness is the Predominant Feature*

Fasciculations	Lower motor neuron diseases
Congenital absence of muscles	Muscular dystrophy
Congenital contractures	Arthrogryposis
Frontal baldness, cataracts, testicular atrophy and myotonia	Myotonic dystrophy
Mental retardation	Duchenne dystrophy, myotonic dystrophy
Electrocardiogram abnormalities	Duchenne dystrophy, myotonic dystrophy, facioscapulohumeral dystrophy
Myotonia	Paramyotonia, myotonic dystrophy, congenital myotonia
Pseudohypertrophy	Muscular dystrophy
Muscle cramping	Myoglobinuria, McArdle's syndrome
Muscle tenderness and dermal lesions	Myositis
Myoedema	Myxedema

patient lifts his head from the pillow or rolls over in bed. In myasthenia gravis the masseter and temporalis muscles may fatigue quickly during chewing. If the orbicularis oculi are involved the patient may complain that he gets soap in his eyes when washing his face. The inability to whistle or to puff out the cheeks are further clues to facial weakness. If the patient is unable to comb her hair or apply lipstick, weakness of the proximal shoulder girdle muscles should be suspected. On the other hand, if she is not able to turn a doorknob or open a jar, distal muscle groups may be involved. Difficulty in crossing one knee on the other, or in arising from a chair or climbing stairs is often an early indication of weakness in the hip and thigh muscles. Foot drop, manifested by stumbling, or the inability to walk on the forefoot, indicates involvement of the distal muscles in the lower extremity. Careful observation of the patient's gait facilitates recognition of specific patterns of weakness. Pathologic locomotion may result from lesions in the upper or lower motor neuron as well as in the muscular system, and each category can often be identified by specific gait patterns that are consistent with the pathologic changes.[12]

TABLE 6.—*Evaluation of Weakness by Anatomical Area*

Corticospinal pathways	Hyperactive stretch reflexes. Increased resistance to passive motion. Abnormal reflexes. Weakness usually greater than atrophy.
Lower motor neuron	
Anterior horn cell	Fasciculation. Hypoactive or absent reflexes. Usually distal or generalized distribution. Atrophy usually in proportion to weakness.
Peripheral nerve	Above plus sensory changes
Myoneural junction—myasthenia gravis	Extraocular musculature usually involved. Fatigue easily following contraction. Strength increases following rest. Variable and fluctuating course.
Muscle fiber	Hypoactive or absent reflexes. Atrophy usually in proportion to weakness. Usually proximal distribution.
Functional	Cogwheel response. Inconsistencies. Hoover sign. Bizarre gait. Slowness of motion. Overflow of activity.

The clinical examination should be supplemented by serial measurements of muscle strength, range of motion, muscle bulk, activities of daily living and physical capacity. An excellent method of assessing the over-all strength of multiple

muscles is by means of functional testing in which the patient's classification is based on the ability and methods used in activities concerned with elevation and ambulation.[11] Such a simple classification can be placed on a reproducible, semiquantitative basis by timing the performance of standard test activities.

Evaluation of weakness in infants and young children is especially difficult and involves a thorough knowledge of normal growth and development. Weakness or hypotonia due to lesions in the corticospinal pathways, cerebellum and brain stem is not always accompanied in early life by exaggerated tendon reflexes, spasticity or pathologic reflexes.[13] Examples of such lesions are early atonic diplegia and congenital athetosis or cerebellar ataxia. Muscular weakness and hypotonia are not always distinguishable since weakness due to a lesion of the distal motor neuron or muscle fiber is often accompanied by hypotonia. This is, however, only true at rest, and there is a pronounced difference in strength between, for example, a child with muscular dystrophy and one with infantile spinal muscular atrophy when an attempt is made to voluntarily contract the muscles.

Before the examination it is necessary to put the child in such a position that the muscle group being tested can lift the appropriate part of the body against gravity. In addition, the muscle group must be made to contract or spontaneously move.[4] During the first six months of life, the various attitudinal reflexes may be utilized to elicit the desired muscle function. The asymmetrical tonic neck reflex demonstrates knee and elbow flexion and extension; Landau's reflex will elicit weakness of the hip, neck and trunk extensors; the grasp reflex can be used to determine weakness of finger flexion; and the Moro reflex will include the involvement of one extremity.

If motor activity is not spontaneously present, noxious stimuli may be used to produce withdrawal. When motor activity is present, relative weakness may be determined by any of several methods. The weak extremity will often resist movement with less force when rapid alternating passive movement is superimposed on spontaneous activity. Information may be obtained by restraining the spontaneous activity of an extremity and noting the force which tends to continue the motion. The shoulder adductors and scapular stabilizers can be tested by lifting the child under the armpits, since the normal spontaneous response is to push down against the examiner's fingers with surprising force. Arm and neck weakness may be determined by pulling the infant from a supine to a sitting position. The weak extremity will straighten out while the normal arm will flex at the elbow. Ambulation and locomotion patterns should also be observed.[5] When ambulation is delayed, abnormal patterns of locomotion—such as rolling, asymmetric crawling, scooting and hitching—are often used to substitute for normal walking. Close observation of these patterns may help in more precise identification of areas of weakness. Hitching, for example, can be performed only with stability of the trunk and upper extremities.

Laboratory Survey

Following the clinical evaluation, a general laboratory survey is indicated especially with reference to thyroid dysfunction, adrenocortical hyperfunction, serum potassium abnormalities, and the response of weakness to edrophonium chloride (Tensilon®). The major diagnostically useful laboratory tests are electromyography, nerve conduction, serum enzyme levels and muscle biopsy. Measurement of serum enzymes and electromyography should be done before the biopsy.

Enzymes such as the glutamic oxaloacetic and glutamic pyruvic transaminases (GOT and GPT), lactic dehydrogenase (LDH), aldolase, and creatine phosphokinase (CPK) are normally present in muscle and other tissues. Increased levels in the serum merely reflect an accelerated release from damaged or diseased tissues. The value of serum enzymes for the diagnosis of muscular diseases depends upon the integrity of other organs, since most enzymes are not specific to muscle and can be elevated in many other diseases. CPK, therefore, has emerged as the most reliable and sensitive chemical indicator of muscle fiber breakdown. Its main advantage is its limited distribution in the human body: It is found in far greater quantity in striated muscle than in any other tissue. The only other common cause of elevation of this enzyme in the serum is acute myocardial disease.

Enzyme levels are elevated in the more rapidly progressive kinds of dystrophy, such as the Duchenne type, and are highest early in the disease.[2] (Table 7). The increase in levels is not constant, however, and the age of the patient and the duration of the disease are factors capable of diminishing enzyme levels in patients with muscular dystrophy. As in many other tests, serial meaurements

TABLE 7.—*Serum Measurements of Creatine Phosphokinase (CPK) in Disorders in which Weakness is the Predominant Feature*

	Levels Elevated
Corticospinal pathways	..
Lower motor neuron	..
Myoneural junction-myasthenia gravis	..
Muscle:	
Duchenne dystrophy	+++
Limb-girdle dystrophy (early)	++
Limb-girdle dystrophy (late)	+
Facioscapulohumeral dystrophy	±
Myotonic dystrophy	±
Distal dystrophy	..
Acute myositis*	+++
Chronic myositis*	+
Congenital myopathies	±
Thyrotoxic myopathy	±

*Transaminases and aldolase often show a greater elevation than CPK.

reduce the chance of error. All of the enzymes, especially the transaminases and aldolase, are increased in dermatomyositis and polymyositis. The degree of rise is generally proportional to the disease activity, and essentially normal levels are often found in chronic myositis or after several weeks of steroid therapy. Little or no enzyme elevation occurs in lesions of the corticospinal pathways, anterior horn cell or peripheral nerve.[8] Occasionally, slight increases in CPK are found in thyrotoxic, nemaline and myotubular myopathy, periodic paralysis, myasthenia gravis and myotonic and facioscapulohumeral dystrophy. Moderate elevations are common in limb-girdle dystrophy when it occurs at an early age. Serum enzyme elevations may also occur in other conditions involving muscle alterations, such as physical exercise, myoglobinuria, surgical operations and crush injuries.

The electromyogram and nerve conduction, when abnormal, provide valuable but not diagnostically specific etiologic information about the weakness (Table 8). Both are normal in patients with lesions of the corticospinal pathways. Electromyograms are usually normal in myasthenia gravis, although findings similar to those observed in myopathy may be found in the late phases of the disease. Of greater significance is the observation that action potentials picked up from muscles that are stimulated with a repetitive current show a rapid diminution in amplitude as stimulation is continued.[1] In normal persons there is no appreciable difference in the amplitude of the response to either a tetanic or twitch stimulation. In some persons the potential amplitude increases rapidly with tetanic stimulation. This finding is regarded as highly suspicious of intrathoracic malignant disease.[10]

The principal contribution of electromyograms in diagnosis of atrophy and weakness due to lesions of the anterior horn cell or peripheral nerve, is the detection of denervation and its anatomic distribution.[9] Denervation is characterized by fibrillation potentials, usually accompanied by sharp waves. Fasciculation potentials may also be found in neuropathic diseases especially when the anterior horn cell is involved. The electromyogram cannot differentiate between lesions of the anterior horn cell and those of the anterior root and the peripheral nerve. To make this distinction, the peripheral nerve conduction velocity or latency is necessary. For example, in anterior horn cell disease such as poliomyelitis, the conduction velocity of the surviving motor nerve fibers is not substantially reduced. In patients with polyneuropathy, however, decided slowing is usually found.

The primary usefulness of electromyograms in evaluation of diseases of the muscle is the detection of abnormal motor units during attempts at volitional contraction. This usually takes the

TABLE 8.—*Electromyographic Findings in Diseases in which Weakness is the Predominant Feature*

	Fibrillation	*Sharp Waves*	*Myotonic Discharges*	*Voluntary Units Amplitude*	*Voluntary Units Duration*
Corticospinal pathways	absent	absent	absent	normal	normal
Lower motor neuron	+++	+++	absent	increased	increased
Myasthenia gravis	absent	absent	absent	usually normal	usually normal
Muscle:					
Dystrophy (early)	rare	rare	absent	often normal	reduced
Dystrophy (far advanced)	+	rare	absent	reduced	reduced
Polymyositis	++	+	pseudo-myotonic discharges	reduced	reduced
Congenital myotonia	absent	absent	+++	normal	normal
Myotonic dystrophy	rare	rare	+++	reduced	reduced

form of a diminution in duration and a reduction in voltage. Often a moderate increase occurs in the incidence of short-duration, low-voltage polyphasic potentials; and frequently there is a low-voltage interference pattern. Fibrillation potentials, with the patient at rest, are not unusual in such diseases as muscular dystrophy and are quite common in polymyositis. Uusally, however, fibrillation is not accompanied by sharp waves in myopathic disorders. Another pattern of potentials is that produced in disorders in which myotonia is a factor. These are characterized by a rapid volley of potentials which wax and wane at a very high frequency.

Muscle Biopsy

The muscle biopsy is the most valuable test in the differential diagnostic study of weakness. The significance of the biopsy, however, depends completely on the care exercised in selecting the muscle from which the specimen is to be taken, the surgical techniques employed, the size of the specimen and the methods by which the tissue is processed for histologic examination.[8] Biopsy of muscle is usually done to differentiate between the various myopathic and neuromyopathic causes of muscular atrophy and weakness or to delineate a generalized disease which only incidentally affects the muscle fibers or the interstitial tissues of muscles (Table 9).

TABLE 9.—*Comparison of Major Histologic Findings During Active Phase of Common Neuromuscular Disorders*

	Muscular Dystrophy	*Polymyositis*	*Neurogenic Atrophy*
Random muscle-fiber atrophy	++	++	..
Group (motor unit) atrophy	..	..	++
Muscle-fiber hypertrophy	++	±	±
Muscle-fiber regeneration	±*	++	..
Central nucleation	++**	+	..
Focal necrosis and phagocytosis	±*	++	..
Inflammatory cell infiltrate	±*	++	..
Connective-tissue proliferation	++	+ to ++	.. (+ late)
Fat-cell proliferation	+ to ++	+	.. (+ late)
Vasculitis	..	+ to ++	..

*May be found early in Duchenne dystrophy.
**Most common in myotonic dystrophy.

In infantile hypotonia, it is often impossible to differentiate among several possibilities without histologic identification. If there is a histologic pattern of group muscle-fiber atrophy surrounded by normal fibers, infantile spinal muscular atrophy is most likely. If there is random muscle fiber atrophy, hypertrophy and regeneration with central nucleation, endomysial connective tissue proliferation and fat-cell proliferation, muscular dystrophy should be considered. A diagnosis of benign congenital hypotonia is probable if the fibers appear to be normal in every respect, although atonic diplegia and severe mental retardation must also be excluded.

Clinically, confusion may also arise between polymyositis with a slow and insidious onset without the characteristic dermal lesions, and limb-girdle muscular dystrophy without a family history. Histologically, random muscle-fiber atrophy may be found in either condition. Polymyositis, however, usually shows less muscle-fiber hypertrophy, central nucleation and fat-cell proliferation and a greater degree of muscle-fiber regeneration and focal necrosis, inflammatory cell infiltration and vasculitis. Occasionally, it is impossible to decide whether the problem is one of slowly progressive dystrophy or polymyositis. A trial of corticosteroids may help in the differentiation.

Weakness is usually proximal in myopathy and distal in neuropathy. Results of biopsy, however, are often crucial in the exceptional rare cases of proximal heredofamilial juvenile muscular atrophy and the equally rare distal form of muscular dystrophy.

REFERENCES

1. Bauwens, Philippe: Introduction to electrodiagnostic procedures, *In:* "Electrodiagnosis and Electromyography," S. Licht, Baltimore, Waverly Press, 1961, pp 171-198.

2. Fowler, Jr., W. M., and Pearson, C. M.: Diagnostic and prognostic significance of serum enzymes. I. Muscular dystrophy, Arch. Phys. Med., 45:117-130, Mar. 1964.

3. Fowler, Jr., W. M., and Pearson, C. M.: Diagnostic and prognostic significance of serum enzymes. II. Neurologic diseases other than muscular dystrophy, Arch. Phys. Med., 45:125-130, Mar. 1964.

4. Johnson, Ernest W.: Examination for muscle weakness in infants and small children, JAMA, 168:1306-1313, Nov. 1958.

5. Johnson, E. W., and Spiegel, M. H.: Ambulation problems in very young children, JAMA, 175:858-863, Mar. 1961.

6. Magee, Kenneth R.: Clinical and pathological observations in neuromuscular disease, A review, Univ. of Mich. Med. Bull., 28:94-105, Mar.-Apr. 1962.

7. Pearson, Carl M.: Differential diagnosis of neuromuscular disease by clinical evaluation, Arch. Phys. Med., 47:122-125, Mar. 1966.

8. Pearson, C. M., and Price, H. M.: Muscle biopsy: Why? How? and When?, Hospital Medicine, 2:34-38, No. 4, Feb. 1966.

9. Rodriguez, A. A., and Oester, Y. T.: Fundamentals of electromyography, *In:* "Electrodiagnosis and Electromyography," S. Licht, Baltimore, Waverly Press, 1961, pp 286-341.

10. Eaton, L. M., and Lambert, E. H.: Electromyography and electric stimulation of nerves in diseases of motor unit, JAMA, 163:1117, Mar. 1957.

11. Vignos, Jr., P. J., Spencer, Jr., G. E., and Archibald, K. C.: Management of progressive muscular dystrophy of childhood, JAMA, 184:89-96, Apr. 1963.

12. Worden, R. E., Johnson, E. W., and Burk, R. D.: Diagnosis of hysterical paralysis, Arch. Phys. Med., 42:122-123, Feb. 1961.

13. Zellweger, Hans: General aspects of muscular hypotonia, Am. J. Phys. Med., 40:177-182, Oct. 1961.